

Editorial Comment

Why Do Beta-Receptor Blockers Decrease Mortality After Myocardial Infarction?*

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Review of major studies. Beta-blockers decrease mortality after myocardial infarction. This statement is no longer controversial after publication of several large well controlled studies (1-4). Yusuf et al. (5) in an extensive review concluded that all available data support the conclusion that beta-adrenergic blocking agents decrease mortality, the incidence of nonfatal reinfarction and sudden death after infarction. The questions that remain concern the mechanism of action and whether this is a class action of all beta-blockers. Singh and Venkatesh (6) suggested that the drugs with significant intrinsic agonist activity such as pindolol and oxprenolol might be less effective. The European Infarction Study (7,8) with oxprenolol is one of the few recent negative studies. This study was stopped prematurely because of a nonstatistically significant increase in mortality in the study group. The reasons for this trend may include fault in the study design or the degree of intrinsic agonist activity in the drug being studied. This negative study is the basis of the arrhythmia analysis presented by Bethge et al. (8) for the European Infarction Study Group in this issue of the Journal.

Explanations of decreased mortality. The major causes of death after myocardial infarction include recurrent ischemia, arrhythmia and left ventricular dysfunction (9). It may be difficult, if not impossible, to separate the effects of ischemia from arrhythmia in the postinfarction patient. Stimulation of beta-receptor blocking agents by catecholamines increases myocardial oxygen consumption and may increase ischemia (10). Obviously, drugs that block the beta-receptors reduce the effects of these catecholamines by decreasing systemic blood pressure, heart rate and myocardial contractility. Other less well documented effects include

those on the coronary microvasculature, collateral blood flow and platelet function (10). The incidence of nonfatal reinfarction was significantly reduced in the timolol trial (3) and a trend toward lower rates of reinfarction was found in the other major trials. These data suggest that postinfarction mortality might be reduced through an effect on ischemia (9). Data pooled from seven of the major trials revealed that beta-blockers caused a 28% reduction in mortality and a 33% reduction in sudden cardiac death. These figures suggest a primary antiarrhythmic effect as the major cause of beneficial action (10). Cyclic adenosine monophosphate (AMP), which accumulates in ischemic zones of experimental myocardial infarction, is arrhythmogenic and its occurrence may be prevented by beta-blockade (11).

Postinfarction ventricular arrhythmia is a well documented marker of increased mortality. Although it is difficult to separate ventricular function from ventricular arrhythmia, it does appear that complex ventricular arrhythmia is an independent marker of mortality (12-14).

Decrease in ventricular arrhythmia shown by several beta-blocker studies. It is clear that beta-blockers have an effect on ventricular arrhythmia in the post-myocardial infarction patient. Koppes et al. (15) noted that 160 mg of propranolol daily reduced the frequency and complexity of ventricular premature beats after myocardial infarction. The Beta Blocker Heart Attack Trial (BHAT) studied ventricular arrhythmia by performing Holter electrocardiographic recordings on all patients at baseline (5 to 21 days after hospital admission) and then on a subgroup of 25% of patients at 6 weeks (16). At 6 weeks, the untreated control group showed an increased prevalence of ventricular arrhythmia, but this increase was blunted in the group taking propranolol. Studies with atenolol showed a decrease in ventricular arrhythmia and specifically a reduction of the R on T phenomenon and repetitive beats (17). Studies by Olsson and Rehnqvist (18) and Cats et al. (19) with metoprolol noted an increase in the frequency and complexity of ventricular premature beats after myocardial infarction. This was counteracted but not abolished by metoprolol. The arrhythmia analysis in the metoprolol study performed by Ryden et al. (20) showed no effect on the occurrence of ventricular premature beats or short bursts of ventricular tachycardia. However, a very striking and important finding was an effect on ventricular fibrillation. The study by Bethge et al. (8) did not find a significant antiarrhythmic effect when oxprenolol, 320 mg daily, was compared with placebo. The only effect noted was a significant decrease in multiform ventricular extrasystoles in the treatment group at 3 and 6 months. A major problem in interpreting these data is the study design, in which only a small percent of the total group had Holter electrocardiographic recordings. A significant number of recordings could not be completed for technical or admin-

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istrative reasons, and many were not available because of the lack of patient cooperation or lack of resources at the study hospital. This raises the possibility that some type of bias may have been introduced into the study. Another possible explanation for this negative result is the drug itself. Oxprenolol, which has intrinsic agonist activity, was also shown to have no detectable antiarrhythmic effect in a trial performed by Wilcox et al. (21).

Does decrease in ventricular arrhythmia explain decrease in mortality? Complex ventricular premature beats are associated with increased mortality and it is generally recognized that many of the beta-blockers decrease these ventricular arrhythmias. It therefore seems reasonable to hypothesize that this antiarrhythmic effect is the mechanism by which the beta-blockers decrease mortality. Capone et al. (22) studied this in the BHAT population. They found that patients with complex ventricular premature beats did have a higher mortality but benefited to the same relative degree from propranolol as did those without complex arrhythmia. Thus, propranolol did not provide any special benefit to those with complex ventricular ectopic rhythm.

Primary effect on ventricular fibrillation. The effect of beta-blockers on ventricular fibrillation has been noted for many years. Recently, Anderson et al. (23) demonstrated an increase in ventricular fibrillation threshold with five different beta-blockers using the anesthetized open chest dog model. They found a further increase in fibrillation threshold after bilateral stellate ganglionectomy. This further shows the dependence of ventricular fibrillation threshold on cardiac sympathetic stimulation. The authors tested five beta-blockers with significant differences in their special properties. Membrane effect and cardioselectivity did not appear to alter results. In low doses, pindolol, a drug with agonist activity, had less effect on ventricular fibrillation threshold compared with timolol. This may be consistent with the observations of Kramer et al. (24), who showed an adverse effect of intrinsic sympathomimetic activity on ventricular fibrillation. The partial agonist activity of pindolol is similar to that of oxprenolol and may provide an explanation of the negative effects on mortality seen in the European Infarction Study. Two of the large beta-blocker studies have provided interesting information concerning ventricular fibrillation that may, in part, explain the mortality results. A subgroup analysis of the BHAT data (25) revealed a lower mortality rate in patients treated with propranolol who had had electrical complications including prior ventricular fibrillation. The metoprolol study (20) showed no effect on ventricular premature beats but a significant effect in preventing ventricular fibrillation. These studies indicate that an antifibrillatory effect may be seen when an antiectopic effect is not. It is possible that microreentry, which is necessary for ventricular fibrillation, may be prevented in situations in which macroreentry, which is necessary for ventricular premature beats, is not prevented (26).

Conclusions. The effect of the beta-blockers on ventricular premature beats, while present, is weak and probably does not explain the drug's beneficial effect on mortality. The effect on ventricular fibrillation threshold is different from the effect on ectopic beats and is the more likely explanation of the increased survival. It would be of interest if the data of the European Infarction Study and the other large beta-blocker studies were examined for effects on ventricular fibrillation.

References

1. Beta Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1982;247:1707-14.
2. Beta Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1983;250:2814-9.
3. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801-7.
4. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. *Lancet* 1981;2:823-6.
5. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71.
6. Singh BN, Venkatesh N. Prevention of myocardial reinfarction and of sudden death in survivors of acute myocardial infarction: role of prophylactic B-adrenoceptor blockade. *Am Heart J* 1984;107:189-200.
7. The European Infarction Study Group. European infarction study (EIS). A secondary prevention study with slow release oxprenolol after myocardial infarction: morbidity and mortality. *Eur Heart J* 1984;5:189-202.
8. Bethge K-P, Andresen D, Boissel J-P, et al. Effect of oxprenolol on ventricular arrhythmias: the European Infarction Study experience. *J Am Coll Cardiol* 1985;6:963-72.
9. Bigger JT, Coromilas J. How do beta-blockers protect after myocardial infarction? *Ann Intern Med* 1984;101:256-8.
10. Koch-Weser J, Frishman WH, Furberg CD, Friedewald WT. B-adrenergic blockade for survivors of acute myocardial infarction. *N Engl J Med* 1984;310:830-7.
11. Pratt C, Lichstein E. Ventricular antiarrhythmic effects of beta-adrenergic blocking drugs: a review of mechanism and clinical studies. *J Clin Pharmacol* 1982;22:335-47.
12. Moss AJ, Davis HT, DeCamilla J, Bayer LW. Ventricular ectopic beats and their relation to sudden and nonsudden cardiac death after myocardial infarction. *Circulation* 1979;60:998-1003.
13. Bigger JT, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM and Multicenter Post-Infarction Research Group. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;69:250-8.
14. Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Shapiro S. Ventricular premature beats and mortality after myocardial infarction. *N Engl J Med* 1977;297:750-7.
15. Koppes GM, Beckmann CH, Jones FG. Propranolol therapy for ventricular arrhythmias 2 months after acute myocardial infarction. *Am J Cardiol* 1980;46:322-8.
16. Lichstein E, Morganroth J, Harrist R, Hubble E for the BHAT study group. *Circulation* 1983;67(suppl 1):I-5-10.
17. Yusuf S, Sleight P, Rossi P, et al. Reduction in infarct size, arrhyth-

- mias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* 1983;67(suppl I):I-32-41.
18. Olsson G, Rehnqvist N. Ventricular arrhythmias during the first year after acute myocardial infarction: influence of long-term treatment with metoprolol. *Circulation* 1984;69:1129-34.
 19. Cats VM, van Capelle FJL, Lie KI, Durrer D. Antiarrhythmic effects on metoprolol in the posthospital phase of myocardial infarction (abstr). *Circulation* 1983;68(suppl III):III-275.
 20. Ryden L, Ariniego R, Amman K, et al. A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. *N Engl J Med* 1983;308:614-8.
 21. Wilcox RG, Hampton JR, Rowley JM, Mitchell JRA, Roland JM, Banks DC. Randomised placebo-controlled trial comparing oxprenolol with disopyramide phosphate in immediate treatment of suspected myocardial infarction. *Lancet* 1980;2:765-9.
 22. Capone R, Friedman L, Byington R. The effect of propranolol on mortality in patients following acute myocardial infarction with complex ventricular arrhythmias (abstr). *Circulation* 1983;68(suppl III):III-294.
 23. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. *Am J Cardiol* 1983;51:1196-202.
 24. Kramer B, Sautter R, Gulker, et al. Influence of intrinsic sympathomimetic activity of B-blockers on ventricular fibrillation threshold and ventricular fibrillation (abstr). *Circulation* 1981;64(suppl IV):IV-125.
 25. Furberg CD, Hawkins CM, Lichstein E. Effect of propranolol in postinfarction patients with mechanical or electrical complications. *Circulation* 1984;69:761-5.
 26. Cardinal R, Janse MJ, van Eeden I, Werner G, d'Almoncourt CN, Durrer D. The effects of lidocaine on intracellular and extracellular potentials, activation, and ventricular arrhythmias during acute regional ischemia in the isolated porcine heart. *Circ Res* 1981;49:792-806.